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Aggravation of Postcardioversion Atrial Dysfunction by Sotalol

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Objectives. **This study determined the effect of sotalol on atrial function after electrical cardioversion of atrial fibrillation.**

Background. **After electrical cardioversion of atrial fibrillation, the Doppler mitral A wave is often diminished, representing impaired atrial contractile function. Sotalol is an effective atrial antiarrhythmic drug with class III and beta-adrenergic blocking properties. Although the negative inotropic effect of sotalol on the ventricle is minimal in patients with normal ventricular function, it may manifest negative inotropy when ventricular function is impaired. We postulated that after cardioversion, when intrinsic atrial function is impaired, sotalol may have an adverse effect on the atrium.**

Methods. **Thirty-seven patients enrolled in a randomized, double-blind study of sotalol for maintenance of sinus rhythm were studied by quantitative Doppler echocardiography within 24 h of electrical cardioversion and, for those still in sinus rhythm, again at 1 month. Doppler variables (E and A wave velocities and integrals) in patients receiving sotalol were compared with those in patients receiving placebo.**

Results. **After electrical cardioversion, peak A wave velocity and A wave time–velocity integral in the 20 patients receiving placebo were reduced compared with normal values. In the 17 patients receiving sotalol (median dose 320 mg twice daily) these variables were further reduced (mean [±SD] peak A wave velocity 19.4 ± 5.5 vs. 38.4 ± 14.7 cm/s, $p < 0.001$ and mean A wave time–velocity integral 1.7 ± 0.6 vs. 3.4 ± 1.4 cm, $p < 0.001$, in sotalol- vs. placebo-treated patients, respectively). Early diastolic filling (E wave variables) did not differ between sotalol- and placebo-treated groups. At 1 month, five sotalol- and six placebo-treated patients remained in sinus rhythm, and A wave variables had increased for the whole group, with a greater increase in sotalol-treated patients.**

Conclusions. **After electrical cardioversion, when atrial stunning is prominent, sotalol has a negative atrial inotropic effect. This effect may be temporary, as suggested by resolution at 1 month. Negative inotropic effects of antiarrhythmic drugs on the atrium should be considered in assessing Doppler variables of left ventricular filling.**

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Sotalol is a class III antiarrhythmic agent with beta-adrenergic blocking properties (1). The most widely studied preparation of sotalol, and the formulation currently available in the United States, is a racemic mixture of dextro and levo isomers (2). The levo isomer is responsible for the beta-blocking aspect of the drug, but the dextro isomer appears to be virtually devoid of this property (3,4). Despite its beta-blocking properties, sotalol has less of a negative inotropic effect on the myocardium than propranolol or other standard beta-blocking agents (5,6), probably because the sotalol-induced lengthening of the action potential duration in cardiac tissue delays the inactivation of the slow calcium channel, thus augmenting myocardial contractility (1,6,7). The hemodynamic response to sotalol in individual patients is dose dependent and is also related to the degree of baseline impairment of the underlying myocardium (8–10). Thus, although several studies have shown minimal effects on indexes of myocardial contractility during short-term therapy in patients with clinically stable disease, longer term use has been associated with the development of clinical congestive heart failure in some patients with a reduced ejection fraction (11).

Sotalol is an effective agent for the prevention of both atrial and ventricular arrhythmias (11–15). Although several studies have documented sotalol's efficacy in terminating or preventing atrial fibrillation (12–15), its effect on atrial function is virtually unexplored. In isolated rat atria sotalol inhibits the positive inotropic response that is normally produced by suprathreshold electrical stimulation (6). To our knowledge, this negative inotropic effect in atrial tissue, which is almost entirely related to the levo isomer (16), has not been studied in either intact animals or humans, and indeed the influence of any cardioactive agent on atrial function is rarely considered. In the present study we examine this concept and report a negative inotropic effect of sotalol on the atrium immediately after electrical cardioversion of atrial fibrillation to sinus rhythm.

Methods

Patient selection. This Doppler echocardiographic study was performed in a subgroup of patients who were enrolled in a multicenter investigation of the ability of sotalol to maintain

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sinus rhythm after cardioversion (Bristol-Myers Squibb Co., unpublished data, on file). Patients were eligible for the antiarrhythmic study if they had had atrial fibrillation sustained for >2 weeks but <1 year. Subjects, all of whom were >18 years old, were excluded from the study for any of the following: 1) concomitant therapy with other antiarrhythmic drugs or with beta-blockers, verapamil or diltiazem; 2) significant conduction abnormalities; 3) recent myocardial infarction or cardiac surgery; 4) uncompensated heart failure; 5) unstable angina or active myocarditis; 6) uncontrolled hypertension; 7) clinically significant chronic obstructive lung disease; 8) insulin-dependent diabetes mellitus; 9) significant hepatic or renal dysfunction.

Patients were allocated in a randomized, blinded fashion, to receive either sotalol or placebo. The initial dose of sotalol was 160 mg twice daily, increasing at 3-day intervals to 240 mg twice daily and then to 320 mg twice daily, unless reversion to sinus rhythm occurred or until side effects limited upward titration. At the end of the 9-day drug/placebo period, those patients remaining in atrial fibrillation underwent electrical cardioversion. It is from this group that the present study draws its subjects.

To be eligible for the echocardiographic study, patients had to remain in sinus rhythm at least 2 h after electrical cardioversion and to have had a full two-dimensional echocardiographic and Doppler study performed within 2 to 24 h after cardioversion. Fifty-one subjects fulfilled these inclusion criteria. Patients were further excluded if they had any of the following features that would confound Doppler interpretation: mitral stenosis (three patients), aortic stenosis (one patient), ejection fraction <35% (one patient), a paced rhythm at the time of echocardiographic study (two patients) or a technically suboptimal Doppler echocardiographic study unsuitable for accurate quantification (i.e., misplacement of sample volume, inappropriate velocity scale, high filter setting, [seven patients]). Thus, the remaining 37 patients form the basis of this report. Of these, 11 patients remained in sinus rhythm at 1 month and underwent a second Doppler echocardiographic study to determine further changes in atrial function.

Echocardiographic measurements. All echocardiograms from the various participating centers were sent to the investigators' site for analysis. Echocardiographic and Doppler measurements were performed off-line by one or both investigators using a computerized digital analysis system (CineView Plus, Freeland Systems). M-mode measurements were obtained according to the American Society of Echocardiography guidelines (17). Left ventricular volumes were calculated by the biplane method of disks from the apical four- and two-chamber views (18) or by the single-plane method in patients who had suboptimal images in either the four- or two-chamber view.

Pulsed Doppler of left ventricular inflow was performed in the apical four-chamber view with the sample volume placed between the mitral leaflet tips and the ultrasound beam lined up in parallel to left ventricular inflow. The mitral velocity

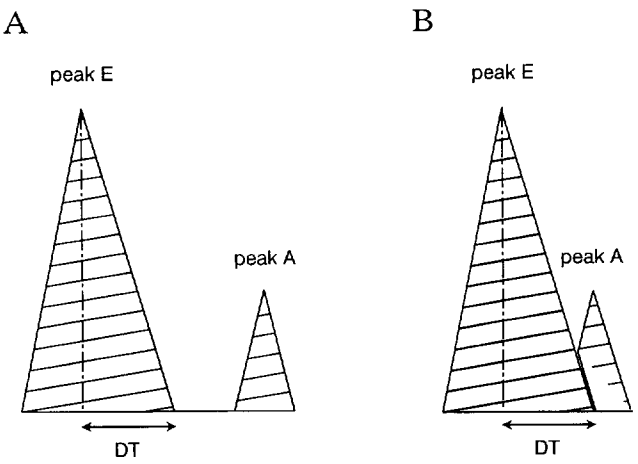

Figure 1. Schematic representation of selected measurements performed on mitral Doppler inflow. **Hatched areas** represent the integrals of the E and A waves, respectively. **A,** At slower heart rate without overlap between E and A waves. **B,** At faster heart rate, with overlap. The E wave deceleration slope is extrapolated to the baseline, and the A wave integral excludes the area of overlap. A = A wave (atrial filling), DT = deceleration time, E = E wave (early diastolic filling). See Methods for details.

tracings were digitized on-screen, following the contour of the Doppler spectral display on at least three consecutive beats to account for beat-to-beat variation. A schematic diagram of the measured mitral Doppler variables appears in Figure 1. Peak E and peak A wave velocities were measured. Acceleration time was measured from the start of mitral inflow to peak E wave. Deceleration time was measured from peak E wave to the time when the extrapolated descent of the E wave intercepted the zero baseline. Heart rate at the time of Doppler acquisition was calculated from the RR intervals of the analyzed waveforms. Total diastolic mitral flow time–velocity integral as well as time–velocity integrals of the E and A waves were obtained according to previously published methodology (19–21). If there was overlap between E and A waves, the E wave integral was considered the area under the E wave extrapolated through the A wave to the baseline. The portion of the A wave integral incorporated in the E wave integral was not included in the A wave integral (20,21). If heart rate was slower and E and A waves did not overlap, the E wave integral was extrapolated through diastasis to the baseline. The remaining small amount of flow during diastasis was not included in the integral of either E or A wave (19). Atrial filling fraction was defined as the A wave integral divided by the total diastolic time–velocity integral.

Statistical analysis. Data are presented as mean value ± SD. Considering the relatively small sample size, normal (Gaussian) distribution of data could not be assumed, and each variable was tested for normality by the Kolmogorov–Smirnov procedure (SigmaStat statistical analysis system, Jandel Scientific Co.). Comparisons between the two study groups used the two-sample t test for variables with normal distribution and equal variance and the Mann–Whitney rank-sum test for

Table 1. Characteristics of Study Patients

	Placebo (n = 20)	Sotalol (n = 17)	p Value
Age (yr)	64 ± 9.5	61 ± 8.6	NS
Duration of atrial fibrillation (days)	133 ± 108	100 ± 54	NS
Left atrial size (M-mode) (cm)	4.8 ± 0.9	5.2 ± 0.6	NS
Left ventricular ejection fraction (%)	57 ± 9	55 ± 8	NS
Significant mitral regurgitation	4/20	2/17	NS

Data presented are mean value ± SD or number of patients.

variables with nonnormal distribution or unequal variance, or both. In comparing repeated measurements performed for the same patient (at 1 day and 1 month postcardioversion), the paired *t* test was used for variables with normal distribution, and the Wilcoxon signed-rank test was used for variables with non-normal distribution. Statistical significance was established at $p < 0.05$.

Results

Patient characteristics. Thirty-seven patients (mean age 63 years, range 41 to 80) were included in the final analysis. The average duration of documented, sustained atrial fibrillation at time of randomization was 118 days. Seventeen patients had been randomized to receive sotalol and 20 to receive placebo. All but four patients were receiving 320 mg of sotalol twice daily at the time of electrical cardioversion.

The main characteristics of the two study groups are detailed in Table 1. Mean age, duration of atrial fibrillation, left atrial size and left ventricular ejection fraction did not differ between groups. Two patients in the sotalol group and four in the placebo group had moderate to severe mitral regurgitation. Six patients in each group had trace or mild aortic incompetence. On the basis of exclusion criteria, none of the patients had mitral or aortic stenosis.

Measurements of left ventricular inflow variables are presented in Table 2. There was a significant difference in both the peak A wave velocity and A wave time–velocity integral between the two groups; each was approximately twice as large

Table 2. Left Ventricular Inflow Doppler and Timing Variables

	Placebo (n = 20)	Sotalol (n = 17)	p Value
Heart rate (beats/min)	70 ± 13	55 ± 6	<0.001
PR interval (ms)	182 ± 24	180 ± 29	NS
Diastolic filling time (ms)	505 ± 195	687 ± 108	<0.001
Total time–velocity integral (cm)	18.9 ± 8.1	18.0 ± 5.0	NS
Peak A wave velocity (cm/s)	38.4 ± 14.7	19.4 ± 5.5	<0.001
A wave time–velocity integral (cm)	3.4 ± 1.4	1.7 ± 0.6	<0.001
Atrial filling fraction (%)	19.7 ± 8.4	10.0 ± 4.0	<0.001
Peak E wave velocity (cm/s)	90.3 ± 32.7	87.0 ± 17.9	NS
E wave time–velocity integral (cm)	14.0 ± 6.2	14.2 ± 4.8	NS
E wave acceleration time (ms)	87 ± 34	89 ± 19	NS
E wave deceleration time (ms)	187 ± 45	217 ± 61	NS

Data presented are mean value ± SD.

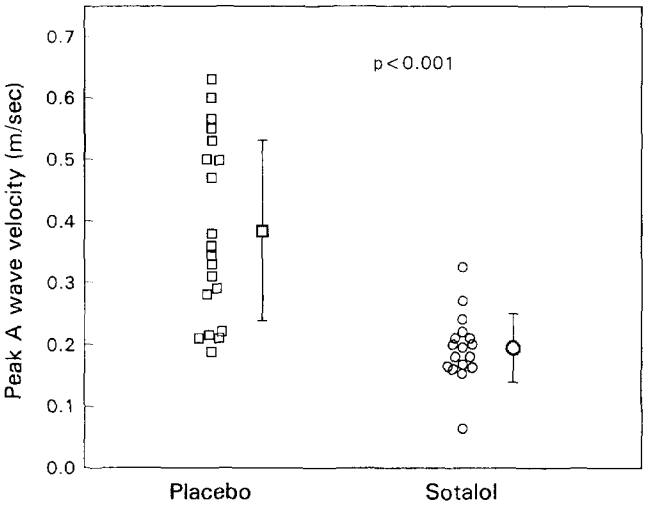

Figure 2. Individual and mean (±SD) values of postcardioversion peak A wave velocity in placebo- **(squares)** and sotalol-treated **(circles)** patients. Mean peak velocity in the sotalol group (0.19 ± 0.06 m/s) was significantly lower than that in the placebo group (0.38 ± 0.15 m/s, $p < 0.001$).

in placebo-treated patients as that in sotalol-treated patients (Fig. 2). In contrast to A wave variables, the peak velocity and time–velocity integral of the E wave, as well as the total diastolic mitral time–velocity integral, were virtually identical in the two study groups. Consequently, the atrial contribution to ventricular filling in the sotalol group was about half that seen in the placebo group (sotalol group 10.0%, placebo group 19.7%, $p < 0.001$). Mean heart rate was 15 beats/min slower in the sotalol group and resulted in a longer diastolic filling period in this group. This is attributed to the direct beta-blocking effect of the drug. The PR interval and acceleration and deceleration times were similar in both groups.

Five sotalol-treated and six placebo-treated patients who continued with their therapy maintained sinus rhythm for at least 1 month after cardioversion. Mean heart rate was 67 beats/min and 49 beats/min in the placebo and sotalol groups, respectively ($p < 0.001$). The individual changes in peak A wave velocity over this period are presented in Figure 3. All except two of these patients had a higher peak A wave velocity at 1 month than immediately after electrical cardioversion. However, sotalol-treated patients had a considerably larger increase in peak A wave velocity (mean increase of 226%) than placebo-treated patients (mean increase of 48%, $p < 0.05$).

Discussion

In recent years, Doppler echocardiography has become a widely used technique for the study of left ventricular filling. Several investigators have noted that immediately after electrical cardioversion, the atrial contribution to ventricular filling is often small or even absent (22–26), an observation attributed to atrial "stunning" as a result of the prolonged arrhythmia (25,26). Serial measurements of Doppler echocardiographic

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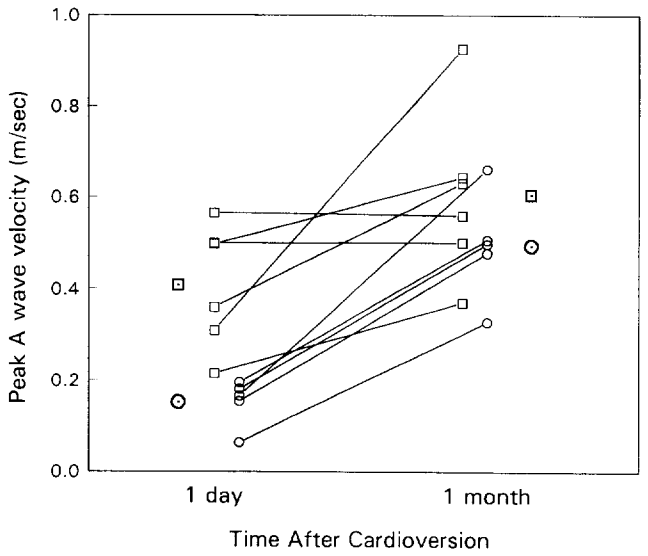

Figure 3. Individual and mean changes in peak A wave velocity from the immediate postcardioversion Doppler study to that performed at 1 month in the 11 patients maintaining sinus rhythm. **Squares** represent patients receiving placebo, **circles** those receiving sotalol. Corresponding mean values are represented by the appropriate **dotted symbol.** Sotalol-treated patients had a greater increase in mean peak A wave velocity than placebo-treated patients (226% vs. 48%, respectively $p < 0.05$).

indexes in those studies revealed a gradual recovery of atrial function over a period of several weeks (25,26) and provide support for the recommendation to continue anticoagulation for 2 to 3 weeks after return of sinus rhythm (27).

A major problem with previous echocardiographic observations is the inhomogeneity of the patients studied. Previous studies did not stratify results by use of antiarrhythmic drugs, although the patients were receiving a variety of therapies, including class IA or IC drugs, beta-blockers or amiodarone. The wide range of therapy may confound the interpretation of postcardioversion Doppler echocardiography because these drugs may have effects on ventricular or atrial function, which could potentially alter transmitral Doppler flow patterns (28–30).

To our knowledge, no previous study has specifically addressed the characteristics of postcardioversion mitral Doppler flow pattern in the drug-free state. In the present investigation the availability of a placebo group permitted us to examine this. We confirmed that, compared with published normal values of A wave velocities and time–velocity integrals (19,31), the mean postcardioversion A wave, in the absence of antiarrhythmic drugs or beta-blockade, is considerably reduced. In addition, a more striking observation was that in subjects treated with sotalol, the postcardioversion mitral Doppler A wave was further reduced compared with the already diminished A wave seen in patients receiving placebo. This difference in left ventricular filling pattern between the two groups was limited to the atrial wave, and no difference in early diastolic filling (E wave) was present. This indicates that sotalol has an isolated effect on late transmitral flow and suggests that the effects of sotalol must be taken into account before it is concluded that a small A wave represents an intrinsic abnormality of atrial function.

Mechanism of effect of sotalol on mitral A wave. Doppler patterns of transmitral flow may be affected by multiple factors that directly or indirectly affect the heart. These include age (19,32–34), heart rate (19,20,34–36), PR interval (19,20), preload (37), intrinsic ventricular properties of relaxation and compliance (28) and (as is the case after cardioversion) impairment of atrial contraction.

Assuming that impairment of atrial function is responsible for the small A wave noted in placebo-treated patients, what factors may account for the further reduction in the atrial contribution to ventricular filling seen in the sotalol-treated group? Randomization ensured a similar duration of arrhythmia in both groups, and the left atrial size did not differ between groups. The PR interval was the same. The age of patients in the two groups had a similar distribution, excluding age-related differences as a factor. Severe impairment of systolic function associated with high ventricular filling pressure may result in a "restrictive" filling pattern characterized by a shortened deceleration time and a small atrial component (38), but this was not the case here because patients with severe ventricular dysfunction were excluded from this study. Indeed, mean ejection fraction did not differ between sotalol- and placebo-treated patients and was in the low-normal range. Furthermore, the similarity of the E wave acceleration and deceleration times in sotalol- and placebo-treated patients implies that significant differences in relaxation and compliance of the left ventricle were not present and thus cannot be responsible for the differences noted in the A wave.

One possible mechanism for the difference in the A wave is the difference in heart rate between the groups. Sotalol-treated patients had a slower heart rate than placebo-treated patients, and heart rate has been noted to affect A wave size, with tachycardia causing a shift of ventricular filling to late diastole, resulting in a greater atrial filling fraction (19,20,35,36). The magnitude of A wave changes associated with heart rate shifts is controversial. In a population-based study, Benjamin et al. (19) found a positive correlation between heart rate and both peak A wave velocity and atrial filling fraction. However, the correlation was weak, and the percent of the variance of peak A velocity attributable to heart rate was only 3%, with the majority of the variance attributable to age. Stewart et al. (36) recently used a multiple regression model to develop prediction formulas for mitral Doppler indexes based on age and heart rate in normal subjects. They found that for every increase in heart rate of 10 beats/min, the expected mean change in peak A wave velocity is only 5.5%. This is far less than the observed doubling of A wave height in placebo-treated patients compared with sotalol-treated patients and suggests that although heart rate differences may have played a minor role, they cannot account for the observed magnitude of the difference in the A wave.

Although the numbers are small, the argument that heart

rate does not play a major role in determining the differences in A waves is further supported by our observations on the 1-month echocardiograms obtained in the sotalol- and placebo-treated patients who remained in sinus rhythm (Fig. 3). Had bradycardia been a major factor in A wave reduction, the difference in A wave should have persisted at 1 month because the sotalol-induced bradycardia was still present. However, although both placebo- and sotalol-treated patients demonstrated the expected increase in A wave height (26,39,40), the mean percent increase in the sotalol-treated patients (226%) was significantly greater than that in placebo-treated patients (48%), resulting in virtual equalization of the A wave between the two groups.

Having excluded all the recognized factors associated with a small A wave, we may reasonably conclude that the diminutive A wave found in the sotalol group primarily reflects a negative inotropic effect of the drug on atrial tissue. Although the predominant antiarrhythmic actions of sotalol result from its class III properties, the drug is a racemic mixture of dextro and levo isomers, and the latter has significant beta-blocking effects. Precipitation of congestive heart failure during long-term drug therapy may occur and has been described in up to 12.5% of patients, the majority of whom had preexisting systolic dysfunction (11). By analogy to systolic dysfunction, we postulate that a baseline atrial abnormality may be a prerequisite for the manifestation of sotalol-induced atrial dysfunction. After restoration of sinus rhythm, an increase in spontaneous echocardiographically visualized contrast has been noted in both the body of the left atrium and the atrial appendage (41). The left atrial appendage may transiently show even less contractility than in the precardioversion state. This phenomenon suggests a "stunning" of the atrium immediately after cardioversion. Such stunning may aggravate the propensity for a negative inotropic effect, as has been demonstrated in an animal model of postischemic myocardial dysfunction (42). In this open chest animal model, dextro sotalol had only a slight effect on contractility of nonischemic myocardium compared with a more marked negative inotropic effect of either levo sotalol or of the racemic compound, whereas in postischemic myocardium all these isomers, including dextro sotalol, produced a cardiodepressant effect (42).

As shown in our placebo group, atrial function was markedly impaired after electrical cardioversion. We propose that, at this stage, the atrium is particularly vulnerable to potential negative inotropic properties of a drug such as sotalol and that the further diminution of A wave height in the sotalol group is a result of this phenomenon. Although we cannot draw firm conclusions regarding the duration of this atrial negative inotropic effect, the disproportionate improvement in A wave height in the small number of sotalol-treated patients restudied at 1 month (compared with the placebo-treated patients) suggests that it is a relatively short-lived phenomenon.

We believe that the beta-blocking properties of the levo isomer of sotalol are the most likely cause of its negative inotropic effect on the atrium. However, as previously indicated, the dextro isomer may impair contractility in certain circumstances (42). Thus, at present, no specific property of racemic sotalol can be definitely stated to be responsible for this effect. Such data await further study.

Limitations of the study. It might be argued that sotalol, by electrically stabilizing the atrium, favored sinus rhythm maintenance in a greater proportion of patients with impaired atrial function, thereby biasing the sotalol group to include a greater number of those with small A waves. We believe this unlikely because there is little evidence to suggest that single Doppler measurements of atrial function correlate with stability of sinus rhythm (43,44). Furthermore, the number of patients in the sotalol and placebo groups was equal, as opposed to the expectation of a greater number of sotalol-treated patients if maintenance of sinus rhythm was significantly better in subjects receiving active therapy.

After cardioversion, the A wave height tends to increase from the immediate postcardioversion period to 24 h later (26,43). The echocardiograms in this study were all obtained within 24 h of cardioversion, but because of logistic difficulties at the various centers, they could not be standardized to be obtained at a more precise time. However, there is nothing to suggest a bias in favor of earlier echocardiograms clustering in one group or another.

Although the small number of 1-month echocardiograms suggested that the difference in sotalol- and placebo-treated patients became less apparent, the present study was primarily limited to the immediate postcardioversion period in which it has clearly demonstrated that a difference exists between placebo- and sotalol-treated patients. It is not known whether, if a larger group of patients had been studied at 1 month, some may have had a persistent drug-induced negative inotropic effect on the atrium. However, this does not affect the conclusions of the study, namely, that the excessive postcardioversion diminution of the A wave in sotalol-treated patients is a function of a negative inotropic effect on the stunned left atrium.

Clinical implications. Attempts have been made to predict long-term maintenance of sinus rhythm from Doppler echocardiograms obtained shortly after cardioversion (43,44), but no reliable variables have been found. These studies did not consider possible effects of antiarrhythmic drugs on the atrium, which, as the present study shows, may be profound. A number of other antiarrhythmic agents used for maintenance of sinus rhythm have negative inotropic effects on the ventricle, such as disopyramide, flecainide and propafenone. Because these agents have the potential to adversely affect the atrium, future attempts to predict recurrence of arrhythmia after cardioversion by examining variables of transmitral Doppler should take into account the use of specific agents.

Delayed recovery of atrial function after cardioversion may be associated with a persistent risk of thromboembolic events until atrial function recovers (27), and it has been suggested that, in the immediate postinfarction period, beta-blockers may predispose to ventricular thrombus formation by virtue of a negative inotropic effect (45). Whether thromboembolic risk might be increased by atrial dysfunction precipitated by widely

used antiarrhythmic drugs is intriguing and warrants further consideration. Finally, recent data (39,40) suggest that improvement of exercise tolerance after cardioversion is delayed, with its time course paralleling the return of atrial function. If it is shown that there is a persistent negative effect of sotalol and other agents on the atrium, then some of the potential benefit of cardioversion on functional capacity may be offset by this action.

Conclusions. There is fertile ground for expanding the investigations of atrial function. However, until data are generated from such studies, we believe it prudent, when evaluating atrial function in an individual patient, to consider the potential effects of negative inotropic drugs on the atrium among the many variables that influence indexes of diastolic ventricular filling.

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